INVASIVE PNEUMOCOCCAL DISEASE IN FIJI

CLINICAL SYNDROMES, EPIDEMIOLOGY, AND THE POTENTIAL IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE

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Abstract: Invasive pneumococcal disease (IPD) epidemiology and the potential impact of the pneumococcal conjugate vaccine in Fiji are documented. The annual incidence was 26.5 and 10.9 in those aged <5 and ≥55 years per 100,000, respectively. The case fatality rate was 9.4% and 67% in <5 and >65 year olds, respectively. One pneumococcal death and case would be prevented in <5 years olds for every 1930 and 128 infants vaccinated with 7vPCV, respectively.

Key Words: invasive pneumococcal disease, serotypes, Fiji

Accepted for publication March 3, 2010.

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Supported by the National Health and Medical Research Council, Australia.

Presented at the 6th International Symposium of Pneumococci and Pneumococcal Diseases, Reykjavik, Iceland, June 8–12, 2008. Abstract number P1–018.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

DOI: 10.1097/INF.0b013e3181ec7ae2

In 2000, over 14 million episodes of serious pneumococcal disease were estimated to have occurred worldwide, with over 800,000 deaths in children <5 years of age.[1] The 7-valent pneumococcal conjugate vaccine (7vPCV) in the United States has led to an impressive reduction in childhood invasive pneumococcal disease (IPD)[2] and has had unanticipated herd immunity effects.[2] The importance of including all ages in the epidemiologic estimates assists in calculating the true economic burden and the likely direct and indirect effects of 7vPCV introduction. No IPD burden studies involving all ages have previously been performed in low or middle income countries.

This study aims to document age-specific IPD in terms of burden and mortality, clinical syndromes, serotype distribution, and the potential coverage of IPD by pneumococcal conjugate vaccines (PCV) in all ages in the Central Medical Division, Fiji, prior to PCV introduction. In addition, the potential impact of 7vPCV on IPD and chest radiograph confirmed pneumonia was estimated.

METHODS

Fiji is a low-middle income country and consists of Indigenous Fijians (57%) and Indo-Fijians (38%) who are of Indian ethnicity. Over 75% of the population lives on one island, Viti Levu, which has 2 medical divisions, the Western and Central divisions. The infant mortality rate (IMR) is 18.4 per 1000 live births (Fiji Ministry of Health Annual Report, 2007). HIV prevalence is <1%.

This was a prospective laboratory-based surveillance study. All invasive *Streptococcus pneumoniae* isolates from the Colonial War Memorial Hospital (CWMH) microbiology laboratory, Suva, from July 1, 2004 to October 31, 2007 were collected. CWMH is the only tertiary referral hospital in Fiji, the referral hospital for serious illness, and the only public hospital that provides microbiology services in the Central division. There are 4 subdivisional hospitals within the catchment, however all children with severe illness are referred to CWMH for medical care. 7vPCV and the 23-valent pneumococcal polysaccharide vaccine are available privately but their current use is negligible.

As a routine, all hospitalized febrile pediatric patients have blood cultures drawn. Hospitalized adult patients with suspected pneumonia may have blood cultures drawn and all patients with suspected sepsis or pyrexia of unknown origin have blood cultures drawn. All suspected meningitis cases have blood cultures and lumbar punctures performed unless contraindicated. Identification of pneumococcal isolates in the CWMH laboratory is based on routine methods. All isolates were stored at −70°C prior to shipment to Westmead Hospital, Centre for Infectious Diseases and Microbiology, Australia for serotyping by Quellung reaction. In addition, any serotype 6A and 6B isolates identified were also serotyped by multiplex-PCR and reverse-line blot assay which are able to detect serotype 6C and 6D.[3,4]

Clinical syndromes were assigned based on presenting symptoms, clinical findings, and laboratory results. Meningitis was defined as *S. pneumoniae* CSF culture positive or a clinical diagnosis of meningitis with positive blood culture. Bacteremic pneumonia was defined as *S. pneumoniae* blood culture positive and physician diagnosis of pneumonia. Pneumococcal sepsis was defined as *S. pneumonia* blood culture positive, no clinical focus of infection, and severe enough to warrant intensive care unit (ICU) admission, and/or newly diagnosed organ failure or cardiovascular instability. Pneumococcal bacteremia without a focus was defined as *S. pneumoniae* blood culture positive without a clinical focus of infection, and no documented evidence of sepsis.

Data were exported to Stata version 9.0 (Stata Corporation, College Station, TX) for analysis. The numerator for the incidence rates was calculated using the number of annual IPD cases and the denominator was the catchment population of the Central Medical division from the 2007 Census. The data from this study based in the Central Medical division was extrapolated to make national estimates for IPD in children aged <5 years assuming the distribution of IPD cases was equal in all divisions. This data was used to calculate the number of 7vPCV preventable episodes of IPD in <5 year olds using the following formula extrapolated from the Hib Rapid Assessment Tool[5]: the estimated annual number of IPD cases/deaths in Fiji was multiplied by the vaccine efficacy (VE) of 97.4% for 7vPCV from published IPD data,[6] multiplied by the local serotype coverage for IPD in <5 year olds (ascertained from our study), multiplied by Fiji's DTP3 immunization coverage of 98% (Fiji Immunization coverage survey, 2009). For chest radiograph confirmed pneumonia in <5 year olds, the number of 7vPCV preventable episodes was calculated using the following formula: the number of cases/deaths were ascertained from previously published Fiji data,[7] and multiplied by the published VE for

chest radiograph confirmed pneumonia of 25.5%,[8] multiplied by an DTP3 coverage rate of 98%.

This study was approved by the University of Melbourne Human Research Ethics Committee and the Fiji National Research Ethics Review Committee.

RESULTS

There were 83 episodes of IPD identified. The annual incidence of IPD was 26.5 and 10.9 in <5 and ≥55-year-old population per 100,000, respectively. The annual incidence by age shows a peak at both extremes of age (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A538). Compared with Indo-Fijians, indigenous Fijians were over 4 times more likely to develop IPD (IRR: 4.3, 95% CI: 2.1–10.3).

Meningitis and bacteremic pneumonia were the commonest clinical manifestations in <5 year olds (Table 1). Bacteremic pneumonia accounted for 56.9% of IPD cases in those aged ≥5 years. Meningitis was more common in the children aged <5 years than those aged ≥5 years. The length of hospital stay was longer in those <5 years compared with the older age group, and a higher proportion (31.3% vs. 3.9%) were admitted to ICU largely because meningitis was a more common clinical manifestation in young children.

There were 17 deaths (CFR 20.5%, 9.4% in those aged <5 years and 53.3% in those aged ≥55 years). The CFR by age group is shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A538. Nearly half of the deaths (47.1%) were in those aged ≥55 years. Of those that died, 47.1% had sepsis. Underlying conditions were present in 64.7% of those that died.

TABLE 1. Clinical Manifestations of IPD Cases by Age (n = 83)

Clinical Manifestations	<5 yr (n = 32) n (%)	≥5 yr (n = 51) n (%)
Meningitis	11 (34.4)	5 (9.8)
Pneumonia	11 (34.4)	29 (56.9)
Sepsis	4 (12.5)	11 (21.6)
Bacteremia without focus	5 (15.6)	4 (7.8)
Pericarditis	1 (3.1)	0
Septic arthritis	0	1 (2)
Unknown	0	1 (2)
Underlying conditions		
Immunodeficiency/ suppression	0	2 (3.9)
Cancer	0	1 (2)
HIV	0	1 (2)
Diabetes	0	7 (13.7)
Congenital heart disease	2 (6.3)	1 (2)
Other cardiovascular disease*	2 (6.3)	11 (21.6)
Chronic lung disease	0	3 (5.9)
Chronic renal disease	0	2 (3.9)
Malnutrition	2 (6.3)	3 (5.9)
Preterm infant	1 (3.1)	NA
Management		
Length of hospital stay in days	11 (5–15)†	6 (3–9)†
For meningitis	14 (10–15)†	3‡
For bacteremic pneumonia	12 (5–21)†	6 (4–8)†
Admitted to ICU	10 (31.3)	2 (3.9)
ICU length of stay in days	4 (3–8)†	6.5 (2–10)†
Deaths (n = 17)	3 (9.4)	14 (27.5)

*Includes ischemic heart disease, hypertension, arrhythmias, cor pulmonale, rheumatic heart disease.

†Median (interquartile range).

‡One case only.

HIV indicates human immunodeficiency virus; ICU, intensive care unit; NA, not applicable.

TABLE 2. Estimated Annual Number of IPD and Hospitalized Chest X-Ray Confirmed Pneumonia Cases and Deaths in Under 5 Year Olds in Fiji, and the Estimated Number of Cases and Deaths Averted if 7vPCV Were Introduced

	Cases	Deaths	Cases Averted	Deaths Averted
IPD	22	2	11	1
CXR-confirmed pneumonia	562	39	140	9
Total	584	41	151	10

IPD indicates invasive pneumococcal disease; 7vPCV, 7-valent pneumococcal conjugate vaccine.

The commonest serotypes were 14 (33.3%) and 6B (13.3%) in children <5 years old, and serotypes 7F (18.8%) and 1 (16.7%) in those ≥5 years (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A538). Six serotypes (14, 6B, 1, 3, 6A, 7F) accounted for 68.8% of all serotypes in children <5 years. The potential coverage of IPD cases by PCV improved as the valency increased (For <5 year olds: 7-valent 53.3%, 10-valent 66.7%, 13-valent 83.3%) (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A538). The 23-valent pneumococcal polysaccharide vaccine (23vPPS) would have no potential additional benefit to the 13-valent PCV in the <5 year olds due to the high prevalence of serotype 6A which is included in the 13-valent PCV but not included in the 23vPPS.

The estimated annual numbers of IPD and chest radiograph confirmed pneumonia cases and deaths in <5 year olds and the number of potentially averted cases and deaths if 7vPCV were introduced are shown in Table 2. For every 1930 infants vaccinated, 1 death would be prevented. For every 128 infants vaccinated one case would be averted.

DISCUSSION

To our knowledge, this is the first report of IPD which includes all ages from a low-middle income country. In this study, IPD is common at both age spectra. The higher rate of IPD between different ethnic groups living within the same geographic region has been described elsewhere and may be related to overcrowding, genetic susceptibility, poorer living conditions, or other unknown factors.

Our data differ substantially from the global burden of disease estimates of 1367 cases per 100,000 <5 year olds and a CFR of 1.9%.[1] Our estimates have fewer cases but higher mortality compared with these estimates. These differences are likely related to the methodologies employed and the reliability of routinely reported data to make global estimates compared with data collected in special studies.

Comparing disease burden rates between geographic sites is difficult due to many differing clinical and laboratory practices. Recently WHO and the PneumoADIP standardized case definitions for the surveillance of pneumococcal disease.[9] Where IPD incidence rates were calculated and countries had similar IMR rates to Fiji, Vietnam, a low-income country, had a higher IPD rate (48.7 per 100,000 <5 year olds),[10] and rural Thailand, a middle-income country, had a similar IPD rate (10.6–28.9 per 100,000 <5 year olds) to our study.[11] There are no published IPD data for all

age groups from other Pacific island countries but our data is likely to be similar and relevant for these regional countries.

In this study, the CFR of IPD in children <5 years was approximately double the reported rate in industrialized countries but similar to that reported in Chile (10%)[12] and Mozambique.[13] For the elderly, the presence of underlying conditions often contributes to the high CFR. In those aged >65 years, the CFR has been found to be <30% in industrialized countries. The CFR in Fiji was much higher at 67% in those aged >65 years. This may be due to our study being hospital based and therefore only including persons with more severe disease who were sick enough to be hospitalized. This may indicate that the true burden of disease is higher and overall CFR is lower than measured in this study. There are no data for this age group to compare with other low-middle income countries. Over half who died in this age group had underlying conditions.

The commonest serotypes causing IPD in <5 year olds in Fiji shows a similar distribution to other countries.[14] The potential coverage of IPD in Fiji by the 7vPCV is low and substantially lower than that reported in the United States prior to vaccine introduction.[15,16] Only hospitalized IPD cases were included in our study which may partially explain this disparity. The 13-valent PCV would provide good universal coverage for all age groups in Fiji due to the addition of serotypes 1 and 7F.

In conclusion, this study provides a reliable baseline of IPD in Fiji in the prevaccination era. Including all ages in the IPD estimate assists in calculating the true economic burden and the likely direct and indirect effects of 7vPCV. The major challenge for Fiji in PCV introduction is the issue of vaccine financing. As Fiji is not GAVI eligible, the cost to fully vaccinate the birth cohort with 3 doses would require the total vaccine procurement budget to increase over 6-fold.

ACKNOWLEDGMENTS

The authors thank Senibua Ketaiwai, the laboratory staff at the Centre for International Child Health (Department of Pediatrics, University of Melbourne and Murdoch Children's Research Institute), Shahin Oftadeh, Lyn Gilbert, the Koronivia Veterinary Research Centre, CWMH, CWMH microbiology laboratory, and all the Fiji Pneumococcal Project staff.

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RESPIRATORY MORBIDITY IN ADULTHOOD AFTER RESPIRATORY SYNCYTIAL VIRUS HOSPITALIZATION IN INFANCY

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Abstract: A prospective >25-year follow-up study evaluated the outcome of patients hospitalized for respiratory syncytial virus (RSV) infection at <24 months of age. Questionnaires were sent to 51 study subjects and to population controls. Self-reported asthma was present in 30% of the former RSV patients, compared with 3.8% of controls. In adjusted analyses, RSV hospitalization was an independent risk factor of adulthood asthma.

Key Words: respiratory syncytial virus, bronchiolitis, pneumonia, asthma, childhood

Accepted for publication March 17, 2010.

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Supported by Kuopio University Hospital (EVO grant, code 440071), The National Foundation for Pediatric Research in Finland, The National Graduate School of Clinical Investigation in Finland, and The Kerttu and Kalle Viik's Foundation.

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DOI: 10.1097/INF.0b013e3181dea5de

Respiratory syncytial virus (RSV) is an important pathogen in lower respiratory infection (LRI) of infants. By 2 years of age, 80% to 90% of all children have experienced at least 1 RSV infection, and 0.5% to 2.0% have been treated in hospital.[1]

We have followed up a group of children hospitalized for viral bronchiolitis and/or pneumonia in infancy in 1981–1982 to 26 to 29 years of age. Viral etiology during hospitalization at <24 months of age was assessed by antibody and antigen assays.[2] In the bronchiolitis group, the prevalence of asthma was 25% at 5 to 6

years of age and 15% at 8 to 10 years of age.[3,4] The respective figures were lower, 13% and 6%, for the RSV positive subgroup. In follow-ups until 18 to 20 years of age, asthma risk was constantly lower after RSV than non-RSV bronchiolitis.[5,6] In patients hospitalized for RSV LRI at <24 months of age, asthma was present, depending on definition, in 17% to 22% at 18 to 20 years of age.[7]

In this questionnaire study, we evaluated asthma, allergy, and respiratory symptoms at 26 to 29 years of age after RSV hospitalization in infancy, by comparing the subjects with RSV hospitalization to population-based controls matched for gender and birth month.

PATIENTS AND METHODS

During 12 months in 1981 to 1982, 127 children were hospitalized for LRI at <24 months of age in the Department of Pediatrics, Kuopio University Hospital (Finland).[2] Chest radiograph was obtained in all cases. RSV etiology of infection was confirmed by antigen and antibody assays.[2] In 2008, a questionnaire was sent to all 51 subjects with early RSV hospitalization, and 40 (78%) answered. The presentation of RSV LRI in infancy was classified by clinical and radiologic criteria: obstruction− filtration+ in 12, obstruction+ infiltration− in 14, and obstruction+ infiltration+ in 14 cases.

Population controls, born like the former RSV LRI patients in the primary area of Kuopio University Hospital and matched for sex and birth month, were obtained by a 4:1 ratio for the 51 cases from the Population Register Centre (Finland). The questionnaire was sent to 204 controls, and 99 answered, from whom a control group of 80 subjects (2 controls for each 40 cases) was constructed.

The questionnaire comprised questions on wheezing symptoms, prolonged (>4 weeks) or night cough apart from infection, doctor-diagnosed asthma, and the use of maintenance and on-demand bronchodilator medication for asthma, and questions on nasal and/or eye symptoms. Doctor-diagnosed asthma was recorded separately for the parents and siblings of the study subjects. Smoking habits were charted, and the daily consumption of 1 cigarette or more during the preceding 12 months was defined as current smoking. The weights and heights were asked for the calculation of body mass index (weight/height square). Body mass index >25 was defined as overweight and >30 as obesity. In case of doctor-diagnosed asthma, the time of asthma diagnosis was recorded: during the preceding 24 months or ever in life. The presence of symptoms and the use of asthma medication were recorded only for the preceding 12 months.

Bronchial asthma was defined by 2 different ways reflecting the certainty of the diagnosis. (1) Doctor-diagnosed asthma: either asthma diagnosed by a doctor during the preceding 24 months, or the use of maintenance medication for asthma during the preceding 12 months. (2) Self-reported asthma: either weekly use of bronchodilators, or asthma diagnosed by a doctor previously and the presence of wheezing symptoms, prolonged cough, or repeated night cough during the preceding 12 months (doctor-diagnosed asthma included by both criteria).

The months when runny or stuffy nose or conjunctival irritation occurred were recorded for the preceding 12 months. Allergic rhinitis and allergic conjunctivitis were defined as nasal or conjunctival symptoms, respectively, apart from infection during the spring or summer time.

The data were analyzed by logistic regression using the SPSS 14.0 statistical package (SPSS Inc., Chicago, IL).

RESULTS

There were 22 (55%) men and 18 women in the former RSV LRI group, and their median age was 27.0 years (range 26.4–28.5). The respective figures in the controls were, because of matching for age and gender, nearly identical (data not shown). As seen in Table 1, overweight, smoking, wheezing symptoms, and self-reported asthma were more common in cases than in controls.

Doctor-diagnosed asthma was present in 5 (13%) cases and in 1 (1.3%) control. These small numbers did not allow any statistical analyses. Self-reported asthma was present in 30% of the cases versus 3.8% in controls (Table 1). The difference between cases and controls was significant in analyses adjusted for age and gender (odds ratio [OR] 11.4), and furthermore for allergic rhinitis (OR 10.96), current smoking, and overweight (14.46). Wheezing symptoms were reported in 35% of the cases versus 16.3% in controls (Table 1). The difference was significant in analyses adjusted for age and gender (OR 2.79), and further for allergic rhinitis (OR 2.65), but not anymore when further adjusted for overweight and current smoking (data not shown).

In the 3 groups formed by clinical and radiologic findings in infancy, the prevalence of self-reported asthma in adulthood varied from 25% to 36% (obstruction+ infiltration+) and that of wheezing symptoms from 29% to 50% (obstruction− infiltration+); however, the differences were not statistically significant (data not shown).

TABLE 1. Questionnaire Data in 40 Young Adults, Hospitalized for RSV Infection in Infancy, Compared With 80 Nonselected Population-based Controls

Questionnaire Data	RSV Infection Group (n = 40)	Population-Based Control Group (n = 80)	OR (95% CI)*
Asthma in parents	11 (27.5%)	11 (27.5%)	1.71 (0.69–4.21)
Asthma in siblings	11/39 (27.5%)	11/39 (27.5%)	2.52 (0.98–6.50)
Body mass index >25 (kg/m^2)	24 (60%)	24 (60%)	3.26 (1.45–7.31)
Body mass index >30 (kg/m^2)	6 (15%)	6 (15%)	0.94 (0.32–2.70)
Current smoking	15 (37.5%)	15 (37.5%)	2.65 (1.12–6.29)
Wheezing symptoms	14 (35%)	14 (35%)	2.79 (1.15–6.75)
Prolonged cough	7 (17.5%)	7 (17.5%)	3.26 (0.96–11.14)
Night cough	5 (12.5%)	5 (12.5%)	2.15 (0.58–7.98)
Allergic rhinitis	16/39 (40%)	16/39 (40%)	1.64 (0.74–3.65)
Allergic conjunctivitis	16 (40%)	16 (40%)	2.24 (0.97–5.20)
Atopic dermatitis	6 (15%)	6 (15%)	1.00 (0.34–2.94)
Self-reported asthma	12 (30%)	3 (3.8%)	11.40 (2.95–44.05)

*Logistic regression adjusted for sex and age.
95% CI indicates 95% confidence interval.

Allergic rhinitis was present in 40% of cases versus 30% in controls. There were no significant differences between the groups by any adjustments. Similarly, there was no association with allergic conjunctivitis. When the combined allergic rhinoconjunctivitis, present in 20 of 40 (50%) cases and 27 of 80 (33.8%) controls, was included in the model, the result remained negative by all adjustments (data not shown).

DISCUSSION

This study was a prospective >25-year follow-up of patients treated in hospital for RSV LRI in infancy. The main result of the study was that RSV hospitalization in infancy increased, independently from confounding factors like allergy, smoking, and overweight, the asthma risk to more than 10-fold in young adulthood. By contrast, there was no significant association between RSV hospitalization in infancy and later allergic rhinoconjunctivitis. From this cohort, former wheezing patients were included in our recent analysis on the outcome after bronchiolitis in infancy,[8] and asthma at 26 to 29 years of age was present in 29% after RSV and in 62% after non-RSV bronchiolitis. In this study focusing on the outcome in adulthood after RSV LRI in infancy, the risk of asthma was highest (36%) after pneumonia with wheezing and the risk of wheezing was highest (50%) after pneumonia without wheezing.

Doctor-diagnosed asthma and self-reported asthma were present in 13% and 30% of the study subjects, compared with 1.3% and 3.8% in the matched population controls from the same area. Eight years earlier, self-reported asthma was assessed by nearly identical criteria, and the prevalence was 22%.[7] This slight increase of asthma prevalence in young adulthood is in line with recent postbronchiolitis follow-ups.[9,10] The prevalence of self-reported adulthood asthma is about 5% in Finland.[11] Thus, the controls of this study represent well the general population, and the risk of adulthood asthma seems to be, depending on the definition, 2.5 fold to even 6 fold after hospitalization for RSV infection in infancy.

Current knowledge about the long-term prognosis of an early RSV infection comes from bronchiolitis studies. In a systematic review, hospitalization for RSV bronchiolitis was associated with wheezing until the age of 6 years but not thereafter.[1] In the only prospective, long-term, controlled study, RSV hospitalization for bronchiolitis at younger than 12 months of age was associated with asthma until 12 years of age,[12] but unfortunately, the later outcome of the cohort has not been published. Our results suggest that the invasiveness of RSV infection, rather than wheezing, play an important role in the outcome.

The strengths of the study are the prospective design, the long follow-up time from infancy into adulthood and a reliable diagnosis of original RSV infection by mainly antigen detection, which at that time in 1981–1982, was available in only a few research laboratories. The participation rate, 78%, was good for a prospective study continuing >25 years. In addition, identical data from population-based controls matched for gender and birth month were collected for this study. Although only 12 subjects finally had adulthood asthma, the power of the study was sufficient to confirm even in adjusted analyses that RSV hospitalization in infancy was an independent risk factor for asthma in adulthood. Because the data were collected by a questionnaire only, the results of the study must be considered with caution.

In conclusion, hospitalization for RSV infection at <24 months of age is, independently from later allergy, smoking and overweight, a significant risk factor of adulthood asthma at 26 to 29 years of age. On the contrary, RSV infection in infancy is not a risk factor for allergic rhinitis or conjunctivitis.

ACKNOWLEDGMENTS

The authors are grateful to Anneli Paloranta, RN, for her skillful work during the study.

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NEPHROPATHIA EPIDEMICA (PUUMALA VIRUS INFECTION) IN AUSTRIAN CHILDREN

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Abstract: From 2000 to 2007, 19 Austrian children (aged 6–18 years) had serologically verified nephropathia epidemica. Common clinical features were abdominal/flank/back pain, fever, nausea, vomiting, headache, and transient visual disturbances. Acute renal failure was present in 18 (95%) patients. All patients recovered completely. Childhood nephropathia epidemica in Austria takes a similar course to those reported for Northern European Puumala virus strains.

Key Words: nephropathia epidemica, puumala virus, children

Accepted for publication March 17, 2010.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

DOI: 10.1097/INF.0b013e3181dfbbe5

Hemorrhagic fever with renal syndrome (HFRS) is caused by hantavirus species and affects approximately 200,000 people worldwide each year, predominantly in Asia.[1] Nephropathia epidemica (NE) is a mild European form of HFRS caused by the Puumala type (PUUV) of hantavirus.[2] In endemic regions in Scandinavia, NE is one of the most common causes of acute renal failure.[2] In Austria, NE is an emerging disease caused by the Alpe-Adrian lineage of the PUUV.[3] The disease was first diagnosed in an adult Austrian patient in 1993. The seroprevalence ranges from 0.08% to 1.8%.[4] In the past, the incidence of hantavirus disease in Austria was probably underestimated as indicated by the continuous spreading of newly recognized PUUV endemic areas.[3]

The natural host reservoir of PUUV is the bank vole (*Myodes glareolus*).[2] The transmission of PUUV from rodents to man is believed to occur through aerosols of virus-containing excretions. The incubation period of NE is 1 to 8 weeks. The ratio of clinical to subclinical infections is 1/5 to 1/10.[2] Typical symptoms of NE include acute onset with fever, headache, abdominal pain, nausea, diarrhea, and visual disturbances. Manifestations of acute tubulointerstitial nephritis are frequent. Thrombocytopenia is typical, and hemorrhagic manifestations occur in about 30% of adult patients.[5]

NE has been thought to be rare in children, and only limited data are available in case series from Northern Europe.[6–8] We report on the first 19 Austrian children with serologically verified recent NE.

MATERIALS AND METHODS

A retrospective analysis of all Austrian children younger than 19 years with NE between 2000 and 2007 was performed. Clinical and laboratory data were collected from 10 Austrian hospitals (University Children's Hospital Graz, n = 6; General Hospital Hartberg, n = 1; General Hospital Deutschlandsberg, n = 2; Children's Hospital Klagenfurt, n = 3; General Hospital Villach, n = 1; General Hospital Wolfsberg, n = 1; University Hospital Vienna/Departments of Pediatrics, n = 2 and Internal Medicine, n = 1; General Hospital Oberwart, n = 1; and Children's Hospital Linz, n = 1).

Serum antibody testing was performed exclusively at the Institute of Virology, University of Vienna. Diagnosis of recent NE was based on the presence of specific serum IgM antibodies by ELISA (recomLine Bunyavirus IgG/IgM, Mikrogen Inc., Germany).

Verbal informed consent was obtained. Demographic data, presenting symptoms, and clinical course were extracted from the patient records, case notes, and electronic medical records after an evaluation protocol. Missing data were completed by telephone conferences with parents/patients.

Leukocyte count, hemoglobin, platelet count, C-reactive protein, plasma electrolytes, creatinine, urea nitrogen, albumin, lactate dehydrogenase, alanine amino-transferase, aspartate aminotransferase, amylase, lipase, and urinalyses were evaluated. Normal ranges of laboratory values were defined as mean ± 2 SD those of healthy children of corresponding age. Glomerular filtration rate was calculated according to the Schwartz formula.[9] Renal ultrasound was conducted in all patients, 4 had percutaneous renal biopsies. Chest radiographs were done in 10 patients. One patient had a lumbal puncture.

RESULTS

The study comprised 19 children (14 boys and 5 girls). The median age was 15 years (range 6–18 years). Exposure to rodent excrements or direct rodent presence was described by all patients. In 16 patients, exposure occurred in weekend cottages (n = 4), or during cleansing activities at their homes (garden house, n = 6; cellar, n = 2; and garret, n = 1), or at mowing the lawn/garden work (n = 3). One patient was exposed by leisure rodent trapping, 2 patients during occupational activities (working in archeological excavations, n = 1 and cleaning cellar, n = 1).

Abdominal pain occurred in all patients (100%). Fever was present in 89% (median, 39.5°C [range 38–41°C]). Duration of fever was a median of 4 (range 2–8) days. Frequent symptoms were nausea (89%), vomiting (84%), and headache (58%). Transient visual disturbances were reported in 47% of our patients. Hemorrhagic manifestations occurred in 21% (hematochezia in 2 patients, epistaxis in 1 patient, and hematemesis in 1 patient). One patient had severe central nervous symptoms with nuchal rigidity, somnolence, and seizure. Duration of hospitalization was a median of 8 (range 3–14) days.

Median blood leukocyte count was 10.1 (range 3.2–19.7) × $10^3/\mu$L. Serum C-reactive protein was elevated in all patients to a median of 47 (range 12–98) mg/L (normal <8mg/L). Thrombocytopenia was present in 84% of patients. Median thrombocyte nadir was 65 (range 25–138) × $10^3/\mu$L on day 4 of 5 (range 2–7) of illness. Thrombocyte counts normalized on median day 8 (range 7–10) of illness.

Plasma lactate dehydrogenase was elevated in 83% of patients, hypoalbuminemia was found in 69%, and hyponatremia in 63%. Aspartate aminotransferase and/or alanine amino-transferase were elevated in 63%, amylase/lipase were elevated in 19% of patients.

Proteinuria (>1g/L) and microscopic hematuria (>10/mm^3) were seen in 100% of patients. Ninety-five percentage of patients developed acute renal failure defined by a raised plasma creatinine value (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A467, which shows the courses of plasma creatinine concentrations). Highest plasma creatinine levels were median, 2.83 (range 1.1–8.6) mg/dL, corresponding to a decrease of calculated glomerular filtration rate to median, 43 (range 10–83) mL/min/1.73 m^2 body surface area (normal >90). Maximum plasma creatinine was measured on median day 6 of illness (range 4–9). There was no correlation between age and severity of renal failure (data not shown). Renal biopsy was performed in 21% and confirmed tubulo-interstitial nephritis. Renal ultrasound was considered to be abnormal in 84%.

Chest radiographs showed lung involvement with signs of pneumonia in 2 of 10 patients (20%). In the patient with central nervous involvement, cerebrospinal fluid showed increased protein content (70 mg/dL) and mild pleocytosis (8 cells/mm^3).

All patients recovered without dialysis. Complete neurologic recovery was seen in the patient with central nervous symptoms.

Follow-up (8 days to 17 months) revealed normal renal function, urinalysis, and blood pressure in 100% of the children.

DISCUSSION

The present report focuses on the first Austrian children with NE. Most of the infections occurred in the southeastern part of Austria (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/A468, which shows the geographic distribution of NE in Austrian children). This distribution corresponds to the areas with the highest seroprevalence rates in the population.[4] A predominance of boys was described in literature and also confirmed in our cohort. The most probable reason was thought to be the more frequent contact of boys with rodents.[5] Adults are

TABLE 1. Common Clinical Findings in Childhood NE (Puumala Virus Infection)

	Lautala[6]	Mustonen[7]	Ahlm[8]	This Report
Country	Finland	Finland	Sweden	Austria
Patients	13	32	32	19
Age (yr)	6–15	4–15	3–15	6–18
Abdominal pain	100%	59%	93%	100%
Fever	100%	100%	100%	89%
Headache	62%	59%	100%	58%
Blurred vision	"common"	25%	—	47%
Hemorrhages	0%	12%	19%	21%
ARF	92%	84%	68%	95%
Dialysis	0%	0%	3%	0%
Pneumonia/x-ray	—	0/15	0/4	2/10
Meningoencephalitis	0%	3%	0%	5%
Recovery	100%	100%	100%	100%

typically exposed to PUUV because of occupational risks as farmers, forestry workers, animal trappers, or mammologists.[2] In our patients, exposure to rodent excrements occurred mainly at home or at weekend cottages in wooden areas during playing or cleansing activities.

Careful patient history is crucial for the suspicion of NE. Particularly in the early phase of NE, symptoms are rather unspecific but follow a typical schedule.[2] Serology becomes positive within the first days of disease and provides an easy step to prove the diagnosis.

In our cohort, the most frequent primary clinical sign was abdominal pain often accompanied by nausea and vomiting. Abdominal pain is observed more commonly in children than in adults.[6,7] In contrast to the other pediatric case series, fever was not documented in all children (Table 1). Headache was described in about half of the patients. In adults, visual disturbances due to a transient myopic shift caused by thickening of the lens are considered pathognomonic of NE.[10] In contrast to Mustonen et al,[7] almost half of our patients described transient visual impairment (Table 1). Thus, blurred vision may provide an important diagnostic hint also in children. In accordance with the case series of Mustonen et al[7] and Ahlm et al,[8] minor hemorrhagic manifestations were also encountered in some patients.

In our series, typical laboratory features were leukocytosis, elevated C-reactive protein, thrombocytopenia, elevated lactate dehydrogenase, hypoalbuminemia, and hyponatremia. Laboratory signs of hepatic or pancreatic involvement were less frequent.

Hematuria and proteinuria occurred in all children. Almost all of them developed acute renal failure. Renal histology showed tubulointerstitial nephritis but lacked NE specific features such as medullary hemorrhage and tubular rupture. The highest plasma creatinine levels were measured around day 6 of illness. All patients recovered without dialysis. As also observed in Northern Europe, normalization of renal function, urinalysis, and blood pressure was documented in all children.[6–8]

About one-third of adult NE patients have symptoms from the lower respiratory tract.[5] Two of our patients examined by chest radiograph had pulmonary infiltrates. In the other pediatric series, lung involvement was not reported (Table 1).

Involvement of central nervous system during acute NE has been described in about 1% of the adult patients.[1] To date, only 1 child with central nervous involvement due to NE has been reported.[7] One of the patients in our series also had meningoencephalitis. In both of them, increased protein values of cerebrospinal fluid pointed to PUUV as the viral agent causing meningitis. Both patients recovered without neurologic sequelae.

To summarize, in Austria childhood NE caused by the Alpe Adrian lineage of PUUV is an emerging infectious disease with good prognosis. Increased awareness of NE among pediatricians may play an important role. Prompt diagnosis by early PUUV serology testing is mandatory to take adequate supportive measures and to avoid unnecessary diagnostic procedures. The clinical course corresponds to a moderate form of HFRS and is comparable to reports from Northern European countries caused by other stains of PUUV.

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TRANSMISSION OF CHILDHOOD TUBERCULOSIS

RISK FACTORS ASSOCIATED WITH AN UNIDENTIFIED INDEX CASE AND OUTBREAK EVOLUTION IN BARCELONA (1987–2007)

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Abstract: The objective of the study was to examine the factors associated with unidentified tuberculosis (TB) index cases (1987–2007) and to describe outbreaks (2000–2007) of childhood TB cases in Barcelona, Spain. Contact tracing seems to be fundamental in index case identification, but improvement could be made among older children and cases of extrapulmonary TB or pulmonary TB with sputum microscopy results.

Key Words: childhood, tuberculosis, transmission, contact tracing, outbreak, epidemiology

Accepted for publication March 18, 2010.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).
DOI: 10.1097/INF.0b013e3181de750d

Childhood tuberculosis (TB) has been generally neglected because TB-infected children are less contagious than adults and thus do not significantly contribute to disease transmission.[1] Nonetheless, a child's risk of TB is principally through an active TB case, reflecting local transmission patterns.[1–3]

Because sputum microscopy confirmation of pediatric TB can be difficult, diagnosis is highly dependent on contact history with a known active TB case.[2,4] Younger children primarily spend time at home and consequently are infected by a household contact frequently; however, school-age or adolescent children may also become infected in a setting outside the household, such as at school or day care.[4] This underscores the importance of aggressive CT and index case identification for pediatric TB case detection and to determine TB transmission and outbreaks within a community.

Although major TB outbreaks involving children have been documented in low-TB incidence regions, further details on contact tracing (CT) and index case identification are limited.[4] The aim of this study was to determine the factors associated with an unidentified index case of pediatric secondary cases reported in Barcelona, Spain, and to describe TB outbreaks which included pediatric cases.

MATERIALS AND METHODS

A population-based cross-sectional design was implemented for the study. We included all TB cases younger than 15 years registered at the TB Prevention and Control Program of Barcelona (TPCPB) who initiated anti-TB treatment between January 1, 1987 (when the TPCPB was created) and December 31, 2007, and resided in the city of Barcelona at the time of TB diagnosis. TB relapse cases (an additional TB diagnosis within 1 year of the previous diagnosis) and nonresidents of Barcelona were excluded. Adult index cases registered with the TPCPB were also reviewed for the outbreak analysis (2000–2007).

A TB case was defined as an individual who presents clinical and/or radiologic findings compatible with TB disease and is prescribed anti-TB treatment. Subjects infected with nontuberculosis mycobacteria were not considered TB cases. An index case was defined as a TB case considered to be a source of transmission to which secondary cases were linked by clinical history, CT, and/or molecular epidemiology. An index case plus one or more secondary cases was considered an outbreak.

The following variables were examined: sex, age (0–4 years, 5–9 years, and 10–14 years), country of origin, inner-city district residence, familial economic difficulties (as stated in the patient's clinical record), year of treatment initiation, diagnosis delay in days between symptom onset and TB treatment initiation, site of TB infection, sputum microscopy results, chest radiologic results, TB treatment outcome, CT completion, and index case identification. Demographic data, clinical characteristics, risk factors, and relationship with index case were also captured for cases within an outbreak.

Differences between categorical variables were compared by the χ^2 or Fisher exact test. Quantitative variables were described using the median and interquartile range (IQR). Potential predictors of an unidentified index case were examined at the bivariate and multivariate levels by calculating the odds ratio with a 95% confidence interval. Factors significant at the bivariate level, as well as those of particular epidemiologic interest, were included in multivariate logistic regression model. Results with P values ≤ 0.05 were considered statistically significant. SPSS Data Editor, Version 18.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

RESULTS

One thousand childhood TB cases were included, accounting for 6.4% of the total cases recorded in Barcelona during the study period. CT was performed on the majority of the cases (n = 918, 91.8%), and an index case was identified for half (n = 478, 47.8%). Case distribution by year and age are presented in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A457.

Ninety-two percent of the cases were born in Spain, 51.2% were male, and the median age was 5 years (IQR: 2–9). Of the 614 (61.4%) children who presented symptoms, the median diagnostic delay was 16 days (IQR: 8–35). Sputum microscopy confirmation was performed for 534 (53.4%) cases, and smear- or culture-positive pulmonary TB was identified in 176 (17.6%) of the total cases. Extrapulmonary TB (ETB) was found in 112 (11.2%) cases, 10 (1.0% of all cases) of whom presented with tuberculous meningitis. The univariate analysis results can be found in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A458.

The bivariate analysis revealed that the following characteristics were significantly associated with the absence of an identified index case: age between 5–9 and 10–14 years, country of origin outside of Spain, inner-city district residence, year of treatment initiation between 1987 and 1997, smear-positive pulmonary TB presentation, ETB presentation, nonsuccessful treatment outcome, and incomplete CT (Table 1). According to the multivariate analysis, the following variables remained statistically significant: age between 5–9 and 10–14 years, birth outside of Spain, treatment initiation between 1987 and 1997, ETB presentation, pulmonary TB presentation with positive or negative microscopy results, and no CT performed (Table 1).

Among the 219 TB outbreaks recorded from 2000 to 2007, 75 (34.3%) involved one or more cases younger than 15 years. The outbreak evolution of outbreaks and characteristics of adult index cases and pediatric secondary cases are presented in Figure, Supplemental Digital Content 3, http://links.lww.com/INF/A459 and Table, Supplemental Digital Content 4, http://links.lww.com/INF/A460, respectively. Ninety-eight secondary cases were children, corresponding to 48.8% of all pediatric cases detected between 2000 and 2007. The pediatric cases represented 18.5% of the cases associated with an outbreak. Fifty-two (69.3%) of the total 75 outbreaks consisted of 2 cases.

DISCUSSION

The study results revealed that the probability of identifying the index case of a pediatric TB case through CT was high; however, identification could be improved among older children and those presenting ETB or pulmonary TB with sputum microscopy results.

The characteristics of the study population are consistent with those found in similar areas and predicted for low-incidence regions.[3,5,6] The presence of smear-positive pulmonary TB cases in our study population lies within the range reported in similar studies, and ETB presentation was slightly less than the 16% estimated for the pediatric population for low-incidence regions region but similar to other estimations from Europe and North America.[3,5–7] One positive indication of control in our population is the few (2%) cases of TB meningitis among cases younger than 5 years.[8]

According to the multivariate analysis, absence of CT corresponds with a 5 times more risk of an absent index case, emphasizing the importance on CT completion and testifying to the effectiveness of local surveillance. Age between 5 and 14 years was also found to be significantly associated with an unidentified

TABLE 1. Factors Associated With the Absence of an Identified Index Case for 1000 Pediatric Tuberculosis Cases. Barcelona, 1987–2007

Variable	n/Total* (%)	Bivariate			Multivariate		
		OR†	CI†	*P*†	OR	CI	*P*
Sex							
Female	244/488 (50.0)	1	—	—	1	—	—
Male	278/512 (54.3)	1.2	0.9–1.5	0.174	1.2	0.9–1.6	0.188
Age (yr)							
0–4	200/466 (42.9)	1	—	—	1	—	—
5–9	173/305 (56.7)	**1.7**	**1.3–2.3**	**<0.001**	**1.9**	**1.3–2.7**	**<0.001**
10–14	149/229 (65.1)	**2.5**	**1.7–3.4**	**<0.001**	**1.9**	**1.4–2.5**	**<0.001**
Country of origin							
Spain	458/917 (49.9)	1	—	—	1	—	—
Other	60/79 (75.9)	**3.2**	**1.9–5.4**	**<0.001**	**3.4**	**1.8–6.2**	**<0.001**
Inner-city residence							
No	144/251 (57.4)	1	—	—	1	—	—
Yes	375/746 (50.3)	**1.3**	**1.0–1.8**	**0.052**	1.2	0.9–1.6	0.301
Familial economic difficulties							
Yes	76/155 (49.0)	1	—	—			
No	446/845 (52.8)	1.2	0.8–1.6	0.391			
Year of treatment initiation							
1998–2007	113/252 (44.8)	1	—	—	1	—	—
1987–1997	409/748 (54.7)	**1.5**	**1.1–2.0**	**0.007**	**2.0**	**1.4–2.8**	**<0.001**
Sputum microscopy per site of tuberculosis							
Not preformed	226/499 (45.3)	1	—	—	1	—	—
Smear-positive PTB	46/71 (64.8)	**2.2**	**1.3–3.7**	**0.003**	**2.4**	**1.4–4.2**	**0.001**
Smear-negative, culture-positive PTB	57/105 (54.3)	1.4	0.9–2.2	0.094	**2.0**	**1.3–3.2**	**0.002**
Smear- and culture-negative PTB	108/206 (52.4)	1.3	0.9–1.8	0.085	**1.6**	**1.1–2.3**	**0.007**
Extrapulmonary tuberculosis	80/112 (71.4)	**3.0**	**1.9–4.7**	**<0.001**	**2.9**	**1.8–4.7**	**<0.001**
Chest radiology							
Unknown	24/39 (61.5)	1	—	—			
Normal	47/82 (57.3)	1.6	0.8–3.0	0.189			
Abnormal, cavitation	22/33 (66.7)	1.3	0.8–2.1	0.254			
Abnormal, no cavitation	429/846 (50.7)	1.9	0.9–4.1	0.077			
Treatment outcome							
Successful	473/925 (51.1)	1	—	—	1	—	—
Other‡	49/75 (65.3)	**1.8**	**1.1–3.0**	**0.019**	1.3	0.7–2.3	0.301
Contact tracing completion							
Yes	451/918 (49.1)	1	—	—	1	—	—
No	71/82 (86.6)	**6.7**	**3.5–12.8**	**<0.001**	**5.1**	**2.6–10.0**	**<0.001**

*Cases with unidentified index case/total cases in category.
†Statistically significant odds ratio (OR), 95% confidence intervals (CI), and $P \leq 0.05$ presented in bold.
‡Treatment prolonged, deceased, transferred out, lost to follow-up.

index case. Other studies have reported similar results and state that a higher rate of identified index cases among children younger than 5 years is likely due to proximity to their parents and limited exposure to many contacts.[2,6] Thus, more exhaustive CT beyond family contacts should be considered to facilitate index case identification among older children.

Our results show that children presenting ETB could be at higher risk of an unidentified index case because of a longer delay in diagnosis and consequently more difficulty in locating an index case.[7] A positive laboratory result could also represent an advanced case of TB, indicating a diagnostic delay.[2] However, sputum microscopy is more likely to be performed on pediatric TB cases without an identified index case; hence, smear- and culture-negative pulmonary TB presentation was also associated with an unidentified index case (Table 1).

According to the outbreak descriptive analysis, a high proportion of pediatric cases were reported as part of an outbreak, supporting data on TB outbreaks in low-TB incidence settings.[2,6] A study on TB transmission conducted in Barcelona between 2003 and 2007 may have resulted in an increased awareness of index and secondary case correlation and therefore improved outbreak detection.[9] In 2005, a large outbreak affecting 7 children staying at a school overnight contributed to the peak in pediatric cases and outbreak prevalence.

Some limitations do exist for this study. First, almost 75% of the cases occurred within the first half of the study period. Second, the outbreak analysis was limited to 2000 to 2007 because the TB outbreak registry was not started until 2000. Finally, the effect of immigration, a documented risk factor for childhood TB, could not be fully assessed because the country of origin of the cases' parents were not available.[1,4,7,10] Country of origin of pediatric cases was included in the multivariate analysis, and immigrant cases were found to be significantly associated with an unidentified index case, possibly because of linguistic and cultural barriers on CT implementation or an index cases outside of Barcelona.[9]

Few publications exist about childhood TB and even less about index case identification and outbreaks.[1,5] This study can serve as an initial assessment of TB transmission among the pediatric population in a large and international city of low-TB incidence.

ACKNOWLEDGMENTS

The authors are grateful for the collaboration of the Public Health Agency of Barcelona Epidemiology Service staff and the

pediatricians, microbiologists, public health nurses, and community health workers in Barcelona. They thank Dr. Ellen Anderson Penno, Western Eye Associates (Calgary, Canada) and Dr. Rabia Ahmed, Department of Medicine, University of Alberta (Alberta, Canada) for their article revisions.

Childhood Tuberculosis Working Group of Barcelona: Imma Badosa, Ana Botía, Roser Clos, Lupe Curiel, Carme Elias, María Antonia Ferrer, Pilar Gorrindo, Eva Masdeu, Jesús Ospina, Nuria Perich, María Jose Santomá, Milagros Sanz, Pere Simón, Angels Talisa, Dolors Villalante (Epidemiology Service, Public Health Agency of Barcelona), Dr. Javier Ballabriga, Dr. Josep María Bertrán, Dr. Mercedes Boronat (Pediatric Department, Hospital Vall d'Hebron), Dr. Rafael Vidal (Pulmonology Department, Hospital Vall d'Hebron), Dr. Josep María Jorba, Dr. María Luisa Roldán (Servicio de Pediatría, Hospital Clínic), Dr. José Luis Barrio, Dr. Nicolás Cobos, Dr. Adela Retana (Pediatric Department, Hospital Santa Creu i Sant Pau), Dr. José Alcaide, Dr. Pere Miret (Centre de Prevenció i Control de la Tuberculosi de Drassanes), Dr. Miguel Barnadas Pico (Pediatric Department, Hospital de San Joan de Deu), Dr. Ventura Rabell (Clínic Infantil Stauros).

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SUBSTANTIAL MORBIDITY FOR HOSPITALIZED CHILDREN WITH COMMUNITY-ACQUIRED ROTAVIRUS INFECTIONS

2005–2007 IMPACT SURVEILLANCE IN CANADIAN HOSPITALS

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Abstract: We describe community-acquired rotavirus illness in 1359 children hospitalized at 12 centers in Canada between January 2005 and December 2007. The median age was 1.5 years. Almost half (48.6%) had significant dehydration, almost one-fifth (19%) had clinical sepsis and 7% had seizures at presentation. The median hospital stay was 3.4 days. Severe clinical presentations are less commonly described in surveillance programs.

Key Words: rotavirus infections, hospitalizations, children, morbidity from rotavirus infections, pediatric hospital surveillance

Accepted for publication March 25, 2010.

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Supported by a grant from GlaxoSmithKline Inc, Merck Canada and the Public Health Agency of Canada's Centre for Food-borne, Environmental and Zoonotic Infectious Diseases and Centre for Immunization and Respiratory Infectious Diseases.

Presented at the International Congress of Chemotherapy and Infection; June 18–21, 2009; Toronto, Ontario, Canada.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

DOI: 10.1097/INF.0b013e3181e20c94

Despite its effect on parents, outpatient visits, and hospital admissions, rotavirus diarrhea in developed countries is generally accepted as a common, relatively benign infection.[1–3] As such, testing is not routinely performed in outpatient settings and since rotavirus is not a reportable disease provincially or nationally, the burden of disease in Canada is unknown.

Currently, there are 2 licensed live attenuated rotavirus vaccines available for purchase in Canada: a human-bovine reassortant vaccine (RotaTeq; Merck and Co, Inc) licensed in August 2006 and a G1P[8] human rotavirus vaccine (Rotarix; GlaxoSmithKline Biologicals) licensed in July 2007. Publicly funded rotavirus immunization programs do not yet exist in Canada. In 2006 and 2007, 3339 and 38,878 doses respectively of RotaTeq were sold for a birth cohort of 722,481 for both years (available at: http://cansim2.statcan.ca/cgi-win/cnsmcgi.pgm), whereas Rotarix was not sold until after 2007 in Canada (personal communication Merck and Co. Inc and GlaxoSmithKline Biologicals). Clinical trials for both vaccines have demonstrated efficacy of 85% or greater against severe disease.[4,5]

The aim of this 3-year surveillance study was to examine the epidemiology of illness associated with rotavirus hospital admissions and to describe the morbidity associated with infection.

METHODS

Active, metropolitan area surveillance for hospital admissions related to infection with rotavirus was conducted by the 12 centers of the Canadian Immunization Monitoring Program, Active (IMPACT). This network of pediatric centers accounts for approximately 90% of the pediatric tertiary care beds in the country, with referrals from all provinces and territories.[6]

The nurse monitor at each center identified all laboratory-confirmed rotavirus cases admitted to the IMPACT hospitals between January 1, 2005 and December 31, 2007 in children 0 to 16 years of age. All centers used the same case finding strategies, case definition, and report form. Identification of rotavirus gastroenteritis was based on laboratory diagnosis and clinical symptoms of acute gastrointestinal infection. Cases were identified on a

prospective basis, while the chart abstraction occurred after discharge. Medical records searches were also used regularly to identify any missed cases of diarrhea or viral gastroenteritis using the following ICD10 codes: A08 (viral and other intestinal infections), A09 (diarrhea and gastroenteritis of infectious origin), K52.9 (noninfectious gastroenteritis), R11 (nausea and vomiting), and R15 (fecal incontinence). Any identified cases were then cross checked for a laboratory diagnosis of rotavirus and cases with a laboratory positive rotavirus diagnosis were included.

The following information was retrieved from the medical record: demographic data, underlying illnesses or immune compromising conditions, details concerning diagnosis, health care utilization, and outcome. The determination of dehydration or dehydration complications was based on health record notes.

All hospital-acquired cases were excluded from this analysis. SAS version 9.1.3 (SAS Institute, Cary, NC) was used for all analyses. Continuous variables were tested with analysis of variance, categorical variables were tested with Fisher exact test and χ^2 tests when appropriate.

RESULTS

A total of 1359 children were hospitalized with laboratory-confirmed, community-acquired rotavirus gastroenteritis at the 12 IMPACT centers over the 3-year period. Seasonal distributions of admissions by age group are shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A477. More than 90% of cases occurred between December and May. The majority of cases (43% [234/537]) in 2005, 42% [173/413] in 2006 and, 49% [199/409] in 2007) occurred in March and April.

Yearly totals and characteristics of the cases are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A478. The majority of cases (63%) occurred in children <2 years. The age distribution was as follows: 129 (9.5%) <3 months, 99 (7.3%) 4 to 6 months, 195 (14.3%) 7 to 11 months, and 431 (31.7%) 12 to 23 months of age. The mean age was 2.4 years while the median age was 1.5 years. This did not differ over the 3 years of surveillance ($P = 0.7$).

Healthy children constituted 61% of admissions, whereas an additional 7% were considered healthy, but had a concurrent acute infection. Among others, the most common underlying health conditions are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A478. Gastrointestinal disorders were responsible for more than 25% of underlying conditions, Crohn's disease (n = 22), and gastroesophageal reflux disorder (n = 19) being most frequent. Older children (10–16 years) were significantly more likely to have underlying health conditions compared with younger children ($P < 0.0001$). None of the 1321 cases whose vaccination status was known had been vaccinated against rotavirus.

Laboratory Detection. Rotavirus was most commonly detected using antigen detection enzyme immunoassays (1034 cases, 76.1%) followed by electron microscopy (245 cases, 18.0%) or both (79 cases, 5.8%). One case (0.1%) was detected by polymerase chain reaction.

Clinical Manifestations. Table 1 describes the clinical manifestations of infection. Vomiting/diarrhea, dehydration, and suspected sepsis were the most frequent presentations among admitted cases. Prior to admission, 1210 (89%) had diarrhea, 1225 (90%) had vomiting, and 923 (69%) had fever. Bloody diarrhea occurred most often in children 10 to 16 years of age (40%, 20/50) all of whom had underlying gastrointestinal conditions. Children <2 years were significantly more likely to present with a clinical picture suggestive of sepsis (22.1%) compared with children between 2 and 16 years (13.7%) ($P < 0.001$) with 50% of children 0 to 3 months of age presenting with sepsis-like picture, a rate significantly higher than among children 4 to 23 months of age ($P < 0.001$). Otherwise, there were no differences in clinical manifestations according to age.

Health Care Utilization and Outcome. Of available data for 1357 children, 191 (14%) had had at least 1 prior outpatient visit elsewhere. Including the emergency room visit that led to the current admission, 897 (68.5%) had 1 visit, 359 (26.4%) had 2, 54 (4%), had 3, and 14 children (1%) had 4 visits to the emergency department. The average length of stay in emergency was 7.9

TABLE 1. Clinical Manifestations and Course of Hospitalized Rotavirus Cases, 2005–2007

Manifestations	Year 2005 N = 537 N (%)	Year 2006 N = 413 N (%)	Year 2007 N = 409 N (%)	Total N = 1359 N (%)
Vomiting/diarrhea without significant dehydration	293 (54.6)	202 (48.9)	146 (35.7)	641 (47.2)
Dehydration	226 (42.1)	195 (47.2)	239 (58.4)	660 (48.6)
Hypotension	23 (4.3)	19 (4.6)	18 (4.4)	60 (4.4)
Sepsis	101 (18.8)	81 (19.6)	76 (18.6)	258 (19)
Seizure	32 (6)	24 (5.8)	39 (9.5)	95 (7)
Bloody diarrhea	25 (4.7)	18 (4.4)	23 (5.6)	66 (4.9)
Other manifestations*	27 (5)	37 (9)	44 (10.8)	108 (7.9)
Mean, median duration of diarrhea prior to admission (min, max)	2.3, 2 (0, 14)	2.5, 2 (0, 21)	2.3, 2 (0, 14)	2.4, 2 (0, 21)
Mean, median duration of vomiting prior to admission (min, max)	2.2, 2 (0, 14)	2.4, 2 (0, 21)	2.2, 2 (0, 12)	2.3, 2 (0, 21)
Mean, median duration of fever prior to admission (min, max) (N = 1350)	1.4, 1 (0, 11)	1.5, 1 (0, 13)	1.5, 1 (0, 17)	1.5, 1 (0, 17)
ICU	17 (3.2%)	17 (4.1%)	14 (3.4%)	48 (3.5%)
Mean, median duration of stay in ICU (min, max)	2.3, 2 (1, 9)	2.5, 2 (1, 8)	2.3, 1 (1, 7)	2.4, 2 (1, 9)
ICU underlying condition	8 (47.1%)	12 (70.6%)	9 (64.3%)	29 (60.4%)
If underlying condition, mean, median duration of stay in ICU (min, max)	2.8, 1.5 (1, 9)	2.4, 2 (1, 8)	2.9, 2 (1, 7)	2.7, 2 (1, 9)
Mean, median duration of hospital stay (min, max)	3.3, 3 (1, 26)	3.6, 3 (1, 46)	3.2, 2 (1, 23)	3.4, 3 (1, 46)

*Altered level of consciousness (41), hematemesis (15), rash (21), cardiac arrest (2), intestinal perforation (1), hepatitis (3), neutropenia or anemia (9), acute renal failure (13), worsening of underlying disease (4), acute hepatic failure (1), elevated lipase (1), and concomitant bacteremia (1) (4 children presented with more than one other clinically significant manifestation).

hours (range: 0–41 hours) with a median of 7 hours. The mean duration of hospital stay was 3.4 days with a median of 3 days (Table 1). A total of 4555 hospital days were used for more than 3 years (1782, 1474, and 1299 days each year). In total, 48 children (3.5%) required intensive care for a mean duration of 2.4 days.

Among 835 children who were healthy and 97 who were healthy with concurrent infections, 49% (460/932) received antimicrobials on admission while 59% (252/427) who had underlying health conditions or who were premature (but otherwise healthy) did ($P = 0.07$).

There were no deaths during the study period from rotavirus infection; all children recovered from infection and were discharged. Over the 3 years of surveillance, 2% (n = 27) were readmitted to hospital within 14 days of hospital discharge and of these 48% (13/27) had an underlying illness.

DISCUSSION

This report describes the first national surveillance for pediatric rotavirus hospitalizations in Canada. The span of surveillance provides evidence of substantial burden of disease and morbidity associated with community-acquired rotavirus and provides some evidence that this infection consumes significant resources, even in tertiary care institutions. Yearly, in these institutions, 1300 to 1800 hospital days are used for treatment of admitted cases with community-acquired rotavirus infection. Consistent with other countries in the developed world, children <2 years represented the majority of children hospitalized in the 3-year period with community-acquired disease.[1,2,7] Assuming at least 85% efficacy of vaccine in infants, vaccination could have prevented approximately 726 admissions and a median of 2178 hospital days over the course of the 3 years in the these 12 institutions in children under 2 years. The length of stay including the stay in the emergency department was just under 4 days per case, in keeping with prior North American and European reports.[1,2,7,8]

As in other northern climates, the rotavirus season over the 3-year period lasted from 20 to 26 weeks or between December and April during each year. Although previously similar in the United States, their rotavirus season has been delayed and shortened with the introduction of rotavirus vaccine.[9] Compared with Switzerland, where 19% were noted to have upper airway infections at admission, 7% of healthy children in our study had concomitant infections.[10] Prevention of rotavirus illness especially during respiratory viral season would not only decrease comorbidity inherent in dual infections but would favorably effect the health care system during peak respiratory viral season.

This 3-year study consistently demonstrated that about one-third of patients hospitalized had significant underlying illnesses. Other similar studies have shown that 13% to 22% of hospitalized patients had underlying conditions.[8,10,11] The presence of older children in this cohort is likely due to the provision of secondary and tertiary care at sites within the network but may also indicate a particularly vulnerable population who are more likely to be hospitalized when ill. Although universal vaccination would initially effect infants, once significant herd immunity is reached, it is expected that transmission to older or more vulnerable groups would decrease.

Despite its pedigree of benignity in developed countries, our data highlighted the morbidity of rotavirus infection (19% of children presented with signs and/or symptoms suggestive of sepsis, 8% presented with other serious manifestations, and 7% with seizures).[7,10] Rotavirus vaccine also has the potential to decrease these less common manifestations that are associated with greater morbidity.

This study has several limitations. The surveillance is not population based and some of the hospitals preferentially manage healthy children as outpatients or at other primary care institutions in the area, thus biasing the cohort to children with underlying diseases or more severe illness. The strength of these data, however, rests with a network that uses standardized data collection, case ascertainment is comprehensive, covers several years and is national in scope allowing for capture of less common presentations.

Universal vaccination programs for rotavirus have potential to decrease disease severity, hospitalization rates, and length of the rotavirus season in Canada.[12]

ACKNOWLEDGMENTS

The authors thank the expert assistance provided by the Monitor Liaison (Heather Samson), the IMPACT nurse monitors and staff of the data center (Kim Marty, Shu Yu Fan, Wenli Zhang, Engy Grove and Debbe Heayn). The Canadian Immunization Monitoring Program, Active (IMPACT) is a national surveillance initiative managed by the Canadian Pediatric Society (CPS) and conducted by the IMPACT network of pediatric investigators.

Investigators and centers participating in this IMPACT project included: R. Morris, MD, Janeway Children's Health & Rehabilitation Centre, St. John's, NF; S. Halperin MD, IWK Health Center, Halifax, NS; P. Déry, MD, Centre Mere-Enfant de Quebec, CHUL, Quebec City, PQ; D. Moore, MD, The Montreal Children's Hospital, Montreal, PQ; M. Lebel, MD, Hôpital Ste-Justine, Montreal, PQ; N. Le Saux, MD, Children's Hospital of Eastern Ontario, Ottawa, ON; D. Tran, MD, The Hospital for Sick Children, Toronto, ON; J. Embree, MD, Winnipeg Children's Hospital, Winnipeg, MB; B. Tan, MD, Royal University Hospital, Saskatoon, SK; T. Jadavji, MD, Alberta Children's Hospital, Calgary, AB; W. Vaudry, MD, Stollery Children's Hospital, Edmonton, AB; and L. Sauvé, MD, BC Children's Hospital, Vancouver, BC.

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LACK OF INCREASE IN VANCOMYCIN RESISTANCE OF PEDIATRIC METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* ISOLATES FROM 2000 TO 2007

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Abstract: We retrospectively studied 306 pediatric methicillin-resistant *Staphylococcus aureus* isolates collected in 2000/2001, 2003, 2005, and 2007 for possible vancomycin minimum inhibitory concentration (MIC) change over time using Etest, agar dilution, and broth microdilution (MicroScan) methods. Vancomycin MICs did not increase. Inducible clindamycin resistance declined significantly (53%–0%, $P < 0.001$). Considerably different proportions of isolates with vancomycin MIC = 2 μg/mL were identified by different laboratory methodologies, suggesting the need for caution in their interpretation and in comparing published data. During this period the proportion of USA300 strains increased dramatically.

Key Words: pediatric, MRSA, vancomycin, D-zone test, inducible clindamycin resistance

Accepted for publication March 25, 2010.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

DOI: 10.1097/INF.0b013e3181e284a6

Vancomycin remains as one of the major options for treating methicillin-resistant *Staphylococcus aureus* (MRSA)-related infections. Although MRSA isolates with resistance to vancomycin (minimum inhibitory concentrations [MICs] ≥32 μg/mL) are rare, some studies have shown a progressive increase in prevalence of MRSA isolates with higher MIC values among clinical isolates over time.[1,2] Others have reported stable vancomycin MICs over time.[3,4] Although the higher MICs in these reports are still within the susceptible range, concern has been expressed that the somewhat higher MICs may be associated with increased likelihood of treatment failure.[5] Assessment of MIC value may be method-dependent to a considerable degree.[6]

In the present study we assessed possible vancomycin MIC change from 2000 to 2007 among pediatric MRSA isolates and compared MIC results generated by using various methodologies including Etest, agar dilution, and broth microdilution (MicroScan). We also assessed changes in susceptibility of MRSA to other antibiotics and examined pulsed field gel electrophoresis (PFGE) types of pediatric MRSA isolates from our hospital between 2000 and 2007.

MATERIALS AND METHODS

We studied 306 MRSA isolates collected at our large children's hospital in 2000/2001, 2003, 2005, and 2007. These included all blood and normally sterile site isolates in each study year as well as all MRSA from nonsterile sites collected in 2000/2001, and the first 70 nonsterile site isolates from each of 2003, 2005, and 2007. Only one isolate/patient was included. MRSA were identified by measuring oxacillin susceptibility by Microscan and confirmed by PBP2 latex agglutination assay. Isolates had been stored at −70°C before testing.

Three methods were used to assess antibiotic susceptibility: (1) MicroScan positive combo panel 29 plates were prepared using the turbidity method, and results were read by the Walkaway 96 instrument (Siemens Healthcare Diagnostics Inc, Deerfield, IL) and verified by manual reading according to the manufacturer's instructions. This panel includes vancomycin, β-lactams, erythromycin, clindamycin, gentamicin, levofloxacin, moxifloxacin, rifampin, trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, daptomycin, quinupristin-dalfopristin, and linezolid. The lowest concentration for vancomycin testing by this method is 0.5 μg/mL; (2) Etest: Vancomycin MIC testing by Etest (Biomerieux, Durham, NC) was performed on all isolates. To limit potential interassay variation, each batch of 20 isolates tested by Etest and for MicroScan included isolates collected during all 4 collection periods, that is, 5 isolates each collected from 2000/2001, 2003, 2005, and 2007, respectively, together with a positive and a negative quality control organism; (3) Agar dilution testing: This was conducted in a single batch in accordance with Clinical and Laboratory Standards Institute standards using vancomycin obtained from Sigma-Aldrich (St. Louis, MO) at 0.25, 0.5, 1, 2, and 4 μg/mL.

Inducible clindamycin resistance was measured by D-zone testing according to the method described by CLSI.

MRSA typing by PFGE was performed on all sterile site isolates and on the first 20 nonsterile site isolates from 2000/2001 and first 30 from 2007. Preparation of bacterial gel plugs and cell lysates was performed as previously described.[7] Whole-cell DNA was digested in 1% agarose gel with *Sma*I enzyme (New England Biolabs, Beverly, MA) at 25°C for 4 hours. Electrophoresis was performed with a CHEF-DRII system (Bio-Rad Laboratories, Hercules, CA) over 21 hours at 14°C with 5 to 13 seconds of linear ramping at 200 V. Reference strains from Network on Antimicrobial Resistance in *S. aureus* included *S. aureus* USA type 100, 200, 300, 400, 500, 600, 700, and 800. All isolates that did not match USA100 to 800 were considered non-USA type. Strains with ≤3 band difference were considered as similar, and those with >3 band difference were considered to be distinct from each other.[8]

Frequencies and proportions were used to summarize parameters of interests. Fisher exact test or χ^2 was applied to evaluate associations between 2 groups. Cochran-Armitage trend test was used to assess trend changes. Logistic regression analysis was applied to evaluate odds ratios of these parameters between any pairs of the study periods. We used SAS 9.1 to conduct analysis and the significant level was 5%.

RESULTS

The total number of *S. aureus* isolates tested was 306. These included all 39 MRSA isolates from normally sterile sites for the study years, 5 isolates from 2000/2001, 12 from 2003, 15 from

TABLE 1. Results Obtained by Testing Isolates With Different Methods

Method	Year	No. Isolates	Vancomycin MIC ≤0.5	Vancomycin MIC = 1	Vancomycin MIC = 2 (%)	MIC_{90} (μg/mL)*	MIC_{50} (μg/mL)*
Agar dilution	2000 + 2001	62	1	60	1 (2)	1	1
	2003	82	1	78	3 (4)	1	1
	2005	85	1	82	2 (2)	1	1
	2007	77	0	75	2 (3)	1	1
MicroScan	2000 + 2001	62	1	45	16 (26)	2	1
	2003	82	1	49	32 (39)	2	1
	2005	85	0	63	2 (26)	2	1
	2007	77	0	43	34 (44)	2	1
Etest	2000 + 2001	62	0	6	56 (90)	2	2
	2003	82	0	12	70 (85)	2	2
	2005	85	0	6	79 (93)	2	2
	2007	77	0	12	65 (84)	2	2

*Minimum inhibitory concentration required to inhibit the growth of 90% (or 50%) of organisms.

2005, and 7 from 2007. The 267 non sterile site isolates included the first 70 MRSA obtained in 2003, 2005, and 2007 as well as all 57 isolates available from 2000/2001.

There was no change in vancomycin MIC_{50} and MIC_{90} values over the study period for any of the 3 methods used (Table 1). When vancomycin MICs were tested by the MicroScan method, the prevalence of isolates with vancomycin MIC of 2 μg/mL ranged from 26% in 2000/2001 to 44% in 2007. Although statistically significant differences were found for the proportions of isolates with MIC of 2 μg/mL collected in 2000/2001 (26%) compared with those in 2007 (44%) ($P = 0.0265$), and between 2005 (26%) and 2007 (44%) ($P = 0.0155$), overall there was not a significant trend of increase in MIC over the entire study period ($P = 0.1196$), and the MIC_{50} and MIC_{90} values did not vary. The MIC results generated by the agar dilution and Etest methods also showed no significant change in isolates with vancomycin = 2 μg/mL over time ($P = 0.9010$ and 0.5996, respectively).

The isolates clearly showed higher vancomycin MIC values with Etest compared with Microscan and particularly when compared with agar dilution (Table 1). By Etest, the prevalence of isolates with vancomycin MIC = 2 μg/mL ranged from 84% to 93% in different years. In contrast, the agar dilution method yielded substantially lower MIC readings, with the large majority (96%–98%) of isolates showing vancomycin MICs ≤ 1 μg/mL. These results are demonstrated in Figure a, Supplemental Digital Content 1, http://links.lww.com/INF/A485, which shows (1) that there was no obvious change in MRSA vancomycin MICs of all isolates over time by any of the 3 methods; and (2) that striking interassay variation exists among the 3 methods used to measure vancomycin MIC values.

Results were virtually identical when only wound and superficial isolates were analyzed (Figure b, Supplemental Digital Content 1, http://links.lww.com/INF/A485).

Table, Supplemental Digital Content 2, http://links.lww.com/INF/A486, demonstrated the MicroScan susceptibility data combining intermediate and resistant for antibiotics other than vancomycin. All isolates were susceptible to daptomycin, quinupristin-dalfopristin, and linezolid. The only statistically significant difference in trend analysis is the decreasing clindamycin resistance over time ($P < 0.0001$).

Although rates of susceptibility to erythromycin did not change significantly over time ($P = 0.1749$), resistance to clindamycin clearly decreased over the period from 2000/2001 to 2007 ($P < 0.0001$). This resistance was reduced from 44% and 49% in 2000/2001 and 2003, respectively, down to 20% in both 2005 and 2007. All clindamycin resistant isolates were also resistant to erythromycin. Interestingly, isolates resistant to erythromycin but susceptible to clindamycin increased from 27% to 65% from 2000/2001 to 2007 ($P < 0.0001$). Prevalence of inducible clindamycin resistance among MRSA isolates measured by the D-zone test declined remarkably from 53% to 0% during our study period ($P < 0.001$) (Table, Supplemental Digital Content 3, http://links.lww.com/INF/A487).

PFGE was performed on all 39 sterile site MRSA isolates, as well as on 20 wound or superficial infection isolates from years 2000/2001 and 30 from 2007. Most isolates in our collection were USA 300, USA 400, or a non-USA PFGE type (Table, Supplemental Digital Content 4, http://links.lww.com/INF/A488) for distribution of PFGE types. Among the wound or superficial infection isolates, USA300 increased markedly from 20% in years 2000/2001 to 90% in year 2007 ($P < 0.0001$), whereas USA400 disappeared and non-USA types markedly declined from 60% to 10% in the same period.

DISCUSSION

Using broth microdilution, Holmes and Jorgensen measured vancomycin MICs and minimal bactericidal concentrations on 240 MRSA blood isolates collected from 1999 through 2006 (patient ages were not specified).[4] They found vancomycin MIC and minimal bactericidal concentration stability and no evidence of increasing values ("creep") over their study period. More recently, Mason et al reported a study of 165 pediatric *S. aureus* isolates, of which 117 were MRSA.[9] Vancomycin MICs were measured by using broth microdilution and Etest methods. A significant increase in vancomycin MICs was found from 2004 to 2005 isolates demonstrated by Etest only.[9]

The results of this study of pediatric MRSA isolates from a large children's hospital showed no significant increase in vancomycin MIC values among isolates obtained during the study period of 2000/2001 to 2007. Our data also show marked variation in MIC values depending on the methodology used. Prakash et al recently reported their observation on similar issues.[6] In their study, the Etest produced MIC values one dilution higher than the values determined by CLSI reference methods of broth microdilution and agar dilution. Mason et al reported similar findings generated with the same 2 methodologies.[9]

The present study differs from the others in the following respects: (1) testing methods for MIC determination included Microscan, which is used routinely by many clinical laboratories, as well as Etest and agar dilution; (2) our study included MRSA isolates exclusively from pediatric patients, from both normally sterile and normally nonsterile sources; (3) we studied the PFGE patterns of many isolates; (4) we assessed susceptibility to a large

panel of antibiotics; and (5) we found remarkable decrease in prevalence of inducible clindamycin resistance over time. The reason for the latter finding is unclear, and data regarding antibiotic prescribing patterns are lacking.

We studied isolates obtained over an 8-year period because assessing the trend of changes in vancomycin MIC values over time provide more reliable data than observing values merely from 1 year to the next.

A limitation of the current study is that we did not test for heterogeneous vancomycin-intermediate *S. aureus*. At this time, the association of these organisms to clinical outcomes is uncertain.[10,11]

In conclusion, vancomycin MICs did not increase among our pediatric MRSA isolates between 2000 and 2007. The facts that USA300 strains increased dramatically and that inducible clindamycin resistance declined markedly from 2000 to 2007 strongly suggest that community-acquired isolates have become predominant.[7,12] Most importantly, very different proportions of isolates with vancomycin MIC = 2 μg/mL are found when different laboratory methodologies are used, suggesting caution in their interpretation and in interpretation of published reports. Etest results most often yielded vancomycin MIC = 2 μg/mL, agar dilution least often, with Microscan yielding intermediate proportions of isolates with MIC = 2 μg/mL.

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COMPLICATIONS OF VARICELLA AFTER IMPLEMENTATION OF ROUTINE CHILDHOOD VARICELLA VACCINATION IN GERMANY

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Abstract: A country-wide sentinel surveillance system was initiated in Germany after implementation of routine varicella vaccination of children >11 months. Sentinel physicians report monthly the number of cases and of severe varicella complications (VC). Case-based questionnaires are completed for VC. We evaluated trend and clinical features of reported VC from April 2005 to March 2009. Reported VC decreased by 81%.

Key Words: varicella, varicella complications, varicella vaccination, sentinel surveillance system

Accepted for publication April 12, 2010.

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All authors declare that they have no competing interests and that no funding was received for this work.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

DOI: 10.1097/INF.0b013e3181e2817f

Although varicella is commonly regarded as a mild disease, serious complications and death occur.[1] In Germany, up to June 2004, vaccination against varicella was only recommended for special risk groups and their contacts and as postexposure prophylaxis. Universal varicella vaccination of all children 11 to 14 months of age was recommended by Germany's Standing Committee on Vaccination in July 2004.[2]

The main objective of this recommendation was reduction of morbidity, and varicella complications (VC) and consequently, the economic burden of disease.[3] Varicella is not notifiable in Germany. Countrywide varicella sentinel surveillance was initiated in April 2005 to evaluate the effects of vaccination. Operative details of the sentinel system have been described elsewhere.[4]

This report describes frequency and type of severe VC found in 4 years of sentinel surveillance.

METHODS

The sentinel consists of a countrywide convenience sample of more than 1000 primary care physicians, of whom 60% are pediatricians and 40% general practitioners (GP). The relative geographic distribution of the sentinel physicians is comparable to the total number of active physicians (~1% of GPs and ~15% of all pediatricians in each region). Participation is voluntary, no incentives are given. Monthly questionnaires are actively requested and contain aggregated numbers (including zero) of varicella cases by age group and on patients with VC. Additional case-based reports for all patients with VC contain information on age, sex, vaccinations status, underlying diseases, type of complication, hospitalization, and outcome.

Questionnaires include case definitions: A case of varicella is defined as a person presenting with a typical clinical picture of maculopapulovesicular rash on skin or mucosa. A severe VC is defined as varicella leading to hospitalization, resulting in oral or parenteral antibiotic or antiviral therapy or accompanied by neu-

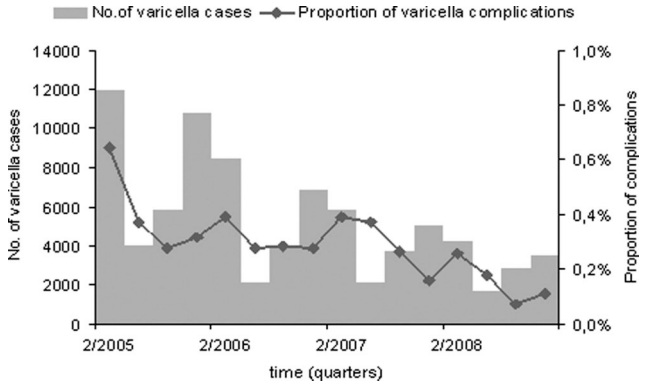

FIGURE 1. Proportion of varicella complications (VC) among all varicella cases reported within the varicella sentinel surveillance system in Germany, 2005–2009.

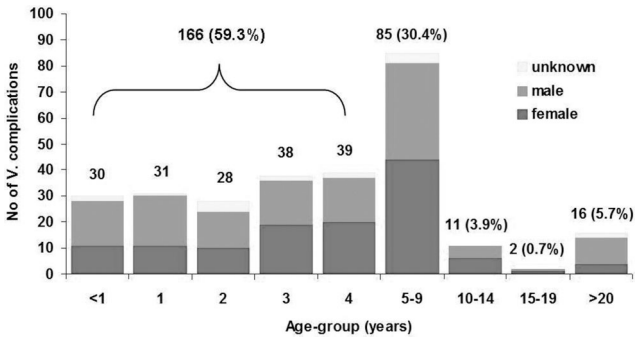

FIGURE 3. Varicella complications (VC) by age-groups and by gender within the varicella sentinel surveillance system in Germany, 2005–2009.

rologic symptoms. We analyzed the frequency and type of VC within the sentinel system in 4 consecutive seasons (April until March of the following year).

For data entry and management MS Access 2007 was used, MS Excel 2007 and Stata version 10 (StataCorp LP, TX) were used for data analysis. Consistency checks were performed by comparing single case reporting of VC via case-based questionnaire with the total number of VC cases reported via monthly questionnaire. Using Pearson χ^2 test statistically significant differences were determined. All P values are 2-sided and the significance level set at $P < 0.05$.

RESULTS

From April 2005 to March 2009, 83,075 varicella cases were reported in monthly questionnaires by 1176 sentinel physicians. While participation of sentinel physicians remained stable, the number of reported varicella cases as well as of VC decreased by 63% and 81%, respectively, when comparing the fourth to the first season (Fig. 1). Cases of varicella and VC peaked in spring (Fig. 2).

Overall, 280 VC were reported via case-based questionnaires (10% less than in the monthly figures) by 150 physicians, corresponding to 0.34% of all reported varicella cases. Decrease in VC was highest (83%) in the age-groups 0 to 4 and 5 to 9 years.

Most VC occurred in 0 to 4 (59%) and 5 to 9 (31%) year olds, 126 (48%) in males (Fig. 3). Of all reported varicella cases the highest proportion of complications occurred in children younger than 2 (24%) and adults older than 20 (5%) years old (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A483).

The type of complication could be identified in 278 VC patients: 144 dermatologic, 27 neurologic and 127 other complications (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A484). Twenty VC patients had more than one type of complication. Bacterial superinfections (n = 108, 36% of VC and 0.13% of all reported varicella cases, respectively) were most common among skin complications, followed by phlegmon (spreading diffuse inflammatory process with formation of pus, n = 15, 5% of VC) and abscess (localized, cavity formed and drainable infected fluid collection, n = 9, 3% of VC). Among "other complication" 47 cases had otitis media (16% of VC and 0.06% of all varicella cases, respectively) and 21 had pneumonia (7% of all VC). Neurologic complications accounted for

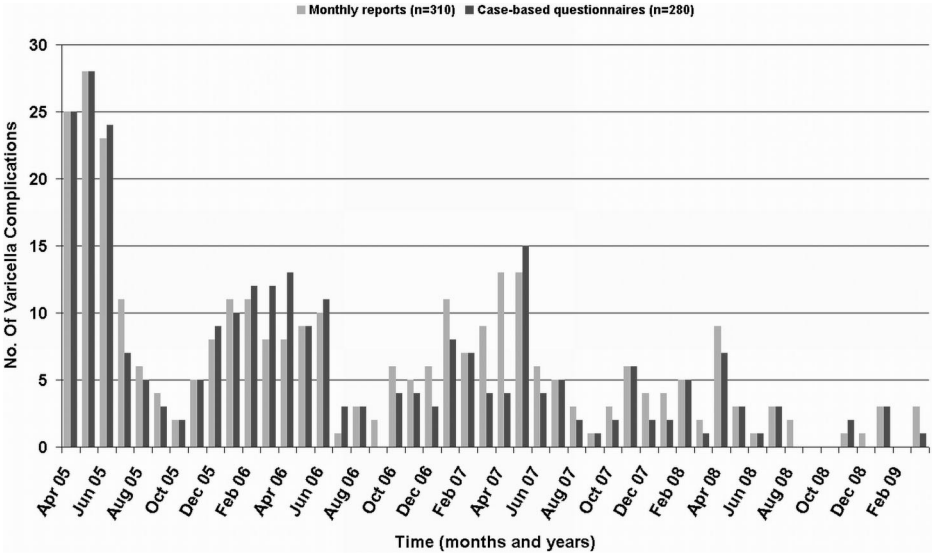

FIGURE 2. Decrease of varicella complications (VC) within the varicella sentinel surveillance system in Germany, 2005–2009.

0.03% of all varicella cases (n = 27, 9% of all VC). A decline in the number of complications over time was observed in all 3 reported categories, but was greatest for skin and for other complications.

Underlying conditions were reported in 30 (11%) VC cases, in 3 more than one condition was present: 12 patients had atopic dermatitis, 11 had chronic diseases such as bronchial asthma, diabetes mellitus, dismorphic syndrome with retarded growth, coronary fistula, multifocal pneumonia with residual bronchitis, nephrocalcinosis, valvular and aortal stenosis, epilepsy, and anemia. Six patients had underlying immune-compromising conditions and 4 were oncology patients. The type of VC did not differ between previously healthy and patients with underlying conditions, but the latter were hospitalized more often (34.0% vs. 27.0%) and showed permanent sequelae more often (16.7% vs. 6.4%) ($P > 0.05$) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A484).

Seventy-one VC cases were hospitalized (median age, 3 years). Patients with neurologic VC were hospitalized more often than patients with dermatologic or other VC (56% vs. 21% and 24%, respectively).

In 94 (33%) cases, the outcome remained unknown, 165 (59%) recovered completely, 19 (7%) developed permanent sequelae and 2 patients died. Comparison of those having permanent sequelae or death (n = 21) with those who fully recovered (n = 165) showed no significant difference by gender, age-groups, complications type, and vaccination status.

Of 277 VC with known vaccination status, 16 (5.8%) were vaccinated, none of them twice. In 6 cases varicella presented within 42 days after vaccination, suggesting vaccination within the incubation period or vaccine related varicella. Ten cases occurred more than 42 days after vaccination (breakthrough cases): 5 presented with otitis media (1 combined with bronchitis and 1 with balanitis) and 2 with bacterial superinfection. Three patients had other complications, 2 of whom were hospitalized because of dehydration and nephrotic syndrome.

DISCUSSION

Our results give the first assessment of severe VC after the introduction of universal varicella vaccination in Germany. Studies estimating the burden of VC before introduction of universal childhood varicella vaccination have relied mostly on hospital data.[5–8]

Our findings are similar to those of Ziebold et al,[8] who demonstrated in a 1-year survey of children younger than 16 years within pediatric hospitals in Germany that the majority of complications occurred in preschool aged children, especially in those less than 1 year of age.

Among hospitalized VC patients reported, the median age was comparable to that estimated by capture-recapture analysis by Liese et al[6,9] before universal varicella vaccination was available in Germany. In this study, an underlying chronic disease was reported in 23% of hospitalized cases, in contrast to 14% among the hospitalized cases reported in the sentinel. However, in both studies the majority of patients with VC or who were hospitalized related to VC were previously healthy persons. This supports the general recommendation for varicella vaccination in childhood rather than a vaccination targeted only at risk groups.

Within the sentinel, the proportion of VC was smaller than estimated by Wutzler et al[7] in a combined seroepidemiologic and analytic study. Possibly our results do not reflect the true proportion because very severe cases present directly at the hospital and are not retrospectively reported by the sentinel physician. Furthermore, physician-based surveillance is known to be affected by reporting bias, possibly leading to underreporting.

The total number of varicella cases and reported complications within the sentinel decreased over time with increasing vaccine uptake. The overall number of VC is low, confirming the success of the varicella vaccination program in Germany. Long term consequences of routine varicella vaccination cannot be determined with the use of our sentinel data. Population-based surveillance programs should be established in the future to monitor further the impact of varicella vaccination on the epidemiology of varicella infections.

ACKNOWLEDGMENTS

The authors thank the participating physicians of the working group for measles and varicella (AGMV) for their contributions to the varicella surveillance in Germany and colleagues from the German Green Cross for good cooperation and their efforts running the sentinel and data management.

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NONTOXINOGENIC *CORYNEBACTERIUM DIPHTHERIAE* AS A RARE CAUSE OF NATIVE ENDOCARDITIS IN CHILDHOOD

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Abstract: We report a pediatric case of negative blood culture pulmonary valve endocarditis caused by a nontoxinogenic *Corynebacterium diphtheriae* biotype gravis and review the literature on this disease.

Key Words: *Corynebacterium diphtheriae*, endocarditis, negative blood cultures

Accepted for publication March 18, 2010.

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DOI: 10.1097/INF.0b013e3181de74ee

Toxinogenic *Corynebacterium diphtheriae* was first identified in 1884, as the causative agent of diphtheria. The disease virtually disappeared after widespread tetanus-diphtheria (Td) immunization in the 1940s.[1] Nontoxinogenic *Corynebacterium diphtheriae* (NTCD) strains have become an increasing cause of invasive infections.[2]

We report a pediatric case of NTCD pulmonary valve endocarditis, and discuss its features compared with those previously reported in both children and adults.

CASE REPORT

A 2-year-old girl from French Guyana was referred to Necker-Enfants Malades with new-onset fever, cardiac murmur, and bilateral pneumonia. She was socially disadvantaged and had a medical history of heterozygotous sickle-cell disease and scabies. She had fully completed the French immunization program, including diphtheria toxoid vaccination.

She first required hospitalization 3 weeks before referral to our center with fever and bronchitis that rapidly evolved into bilateral pneumonia that failed to respond to cefotaxime, netilmicin, and vancomycin therapy. The direct examination of pleural effusion revealed Gram-positive bacilli that failed to grow on standard microbiologic culture media (5% sheep's blood agar and chocolate agar). Three blood cultures remained sterile. A transthoracic echocardiography (TTE), performed because of a newly diagnosed diastolic murmur, revealed a pulmonary valve vegetation. The patient was then referred to our center.

On presentation, the patient was febrile (39.0°C), and physical examination revealed III/VI diastolic murmur without cardiac dysfunction or shock. She was tachypneic, and she had bilateral basal crackles and decreased vesicular breath sounds on pulmonary auscultation. She had scars on both legs. No obvious primary source of infection was found. Extensive laboratory examinations only showed an elevated C-reactive protein value (385 mg/L) associated with leukocytosis (white blood cells count, $26{,}000 \times 10^9$ cells/L). Bilateral basal pneumonia without cardiac silhouette enlargement was found on thoracic radiographic examination. TTE showed a voluminous (2.5 cm) and mobile vegetation on the pulmonary valve associated with mild regurgitation and pericardial effusion. Other valves were not affected. Right and left ventricular functions were normal. No pulmonary hypertension was noted. Cerebral and thoracoabdominal computed tomography (CT) confirmed bilateral basal pneumonia and did not reveal any embolic lesion in the brain, liver, spleen, or kidneys. Three blood cultures were drawn, and antimicrobial therapy was changed to cefotaxime, gentamicin, and vancomycin.

Pulmonary valve resection without valve replacement was performed on day 2 because of concern for embolization. Surgical examination revealed a 2.5-cm vegetation with severe valve destruction. No other lesion was found except for mild pericardial effusion. Direct examinations and cultures of valve biopsy and pericardial effusion were negative.

She did well postoperatively and was extubated on the first postoperative day. Because all microbiologic studies were negative, cefotaxime, gentamicin, and vancomycin were continued.

Fever persisted despite surgery, and she developed worsening tachypnea without hypoxemia and marked mental status changes on postoperative day 4. The C-reactive protein was 381 mg/L, and white blood cells count was $31{,}000 \times 10^9$ cells/L. Physical examination and a thoracic radiograph were otherwise unchanged. TTE failed to demonstrate any new infectious process. Thoracic CT revealed persistent bilateral basal pneumonia. Peripheral and central catheter blood, respiratory, and urinary samples were sent for stains and cultures. Nosocomial infection was suspected, and the antimicrobial regimen was modified to imipenem, amikacin, and vancomycin. All cultures remained sterile.

On day 11, 16s polymerase chain reaction (PCR) examination of the resected valve revealed a *Corynebacterium diphtheriae* biotype gravis. Polymerase chain reaction testing performed at the Centre National de Référence des Corynebactéries did not find the diphtheria toxin gene. The antimicrobial regimen was modified to amoxicillin, gentamicin, and rifampin intravenously. Skin and nasopharyngeal cultures for *Corynebacterium diphtheriae* were negative (none of her family members was tested).

She became afebrile on day 11 and clinically improved. Thoracic CT performed on day 20 revealed a new peripheral embolic lesion in the right lung but demonstrated the improvement of the initial pneumonia. Blood cultures remained sterile, and multiple TTE examinations failed to reveal new changes. She was discharged after 30 days, and intravenous antimicrobial therapy was continued for a total duration of 6 weeks. At 3-month follow-up, she remained asymptomatic except for a mild pulmonary regurgitation murmur. The patient will require lifelong follow-up and presumably further intervention.

DISCUSSION

Nontoxinogenic *Corynebacterium diphtheriae* strains have increasingly been identified as a cause of pharyngitis and cutaneous infection and of invasive diseases including bacteremia, septic arthritis, splenic abscesses, and endocarditis.[2] Nontoxinogenic *Corynebacterium diphtheriae* carriage and infections have been most frequently associated with homelessness,[3] intravenous drug use,[4] and alcoholism[5]; infection has been described in Australian Aboriginals as well.[2] Reports of NTCD have been more frequent because the widespread use of Td vaccine that may have exerted selective pressure on nontoxinogenic strains. Alternatively, the increased incidence may result from increased pathogenicity of NTCD[6] and the growing number of socially disadvantaged individuals globally.[3] The studies around the globe have demonstrated that there are a wide diversity of NCTD clones but typically on single clone, predominates as the cause of infection or nasal colonization in a particular geographic area and a specific population.[2–4] This frequent and persistent nasal carriage in man and the potential of NTCD to result in invasive disease may cause a serious public health threat, especially, because it is possible for the NTCD to acquire the toxin gene in the context of low immunization rates.[7,8]

Cases of endocarditis reported in the English language literature were identified by a Medline search with the following terms: *Corynebacterium diphtheriae*, infection, and endocarditis. All articles retrieved by the search, and subsequent relevant articles were reviewed by a single author (D.S.). Only cases with documented endocarditis (conclusive echographic or pathologic findings) were included. Since the first description by Howard[9] in 1893, 59 cases of *Corynebacterium diphtheriae* endocarditis have been reported. Most cases occurred in young previously healthy individuals and typically involved the left-heart valves. Vegetations are frequently large and prone to embolize, whereas valvular lesions are typically destructive. This may explain the high mor-

bidity and mortality. Cardiac surgery was performed in 43% of the patients, and the mortality rate reached 41%. Septic arthritis is found in 25% of cases. Few patients had a documented primary source of infection. In the study by Tiley et al,[2] 5 of the 7 reported patients had history of pharyngitis in the preceding days. Cutaneous colonization or infection may also have been the primary source as demonstrated by the frequent association with intravenous drug use.[4] Most patients were treated with penicillin and an aminoglycoside.

The present report highlights some features of NTCD endocarditis. First, it occurred in a previously healthy young girl, living in poor socioeconomic conditions. Second, the progressive course of the disease with a destructive valvular lesion and multiple embolic events reflect the difficulty to manage NTCD endocarditis. Presumably, the initial bilateral basal pneumonia in our patient resulted from septic pulmonary emboli. It is unclear why she had persistent fever and clinical decline despite surgery, and the use of vancomycin, cefotaxime, and an aminoglycoside. The recommended regimen of penicillin and an aminoglycoside is based on expert opinion.[7] Both tolerance and paradoxic bactericidal effect (Eagle effect) have been described in animal models of NTCD endocarditis.[10,11] Rifampin was associated with rapid eradication of nasopharyngeal carriage of *Corynebacterium diphtheriae* in 1 study.[12] Rifampin is not recommended as first-line monotherapy because of resistance[3] but may be useful in combination with penicillin. We believe that pulmonary septic emboli with persistent or newly formed vegetation could have played a role in the observed therapeutic failure in the postoperative period. Angiographic pulmonary CT scan could have been helpful to investigate this hypothesis.

ACKNOWLEDGMENTS

The authors thank the Centre National de Référence des Corynebactéries for the help in strain identification and assessment of toxin in our isolate. The authors also thank Michael Ison for reviewing the final manuscript.

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